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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/721,550	11/22/2000	Norbert Reich	510015-234	3451

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EXAMINER
TAYLOR, JANELL E

ART UNIT	PAPER NUMBER
1634	14

DATE MAILED: 09/17/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/721,550	REICH, NORBERT	
	Examiner	Art Unit	
	Janell Cleveland Taylor	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 June 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-40* is/are pending in the application.

4a) Of the above claim(s) *33-36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-7,10-20,22-32,37 and 38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Detailed action* .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. The request filed on July 10, 2002 for a Request for Continued Examination (RCE) under 37 CFR 1.114 is acceptable and an RCE has been established. An action on the RCE follows.

Claim Objections

2. Claims 34-35 are objected to because of the following informalities: claim 34 still depends from canceled claim 33, and claim 35 is not properly marked to show amendment to depend from claim 31 in the "marked up version" of the claims. In order to further prosecution, the claims 34-35 will be examined as if they depend from claim 31. Appropriate correction is required, however.

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 1, 4, 5, 10-13, 16-17, 19-20, 22-27, 29-32, and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over McCasky in view of McGall et al.

McCasky et al teaches an array which has a labeled probe attached. "Typically, a... probe is linked to a solid support and a target nucleic acid (e.g., a genomic nucleic acid, an amplicon, or, most commonly, an amplified mixture) is hybridized to the probe.

Either the probe, or the target, or both can be labeled, typically with a fluorophore. Where the target is labeled, hybridization is detected by detecting bound fluorescence. Where the probe is labeled, hybridization is typically detected by quenching of the label. Where both the probe and the target are labeled, detection of hybridization is typically performed by monitoring a color shift resulting from proximity of the two bound labels..." (Col. 23, lines 38-45).

McCasky does not teach nucleotide analogs, or an array divided into quadrants, or a method wherein the levels of label are expressed twice and compared, or labeled probes achieved by non-amplification steps, or the amount of probe on the microarray.

As disclosed above, McGall et al. teaches "Oligonucleotide analogue arrays attached to solid substrates...target nucleic acids that comprise nucleotide analogs are bound to oligonucleotide analogue arrays." (Abstract). McGall also teaches that the "oligonucleotide probe arrays also comprise nucleotide analogues" (Col. 2, lines 50-51). McGall also teaches that the substrate may be a bead. (Col. 14 line 46). McGall also teaches detection by labeling probe molecules. (Col. 12 line 40).

It would have been obvious to combine McCasky and McGall because McGall teaches that "oligonucleotide analogues are resistant to hydrolysis or degradation by nuclease enzymes such as RNase A." This would have protected the probe from degradation.

McGall et al. does not specifically teach quadrants on the microarray, or the amount of probes on the microarray. McGall also does not teach measuring fluorescent levels before and after hybridization.

It would have been obvious to one of ordinary skill in the art to separate the areas of the microarrays into different quadrants having different probes. This was, in fact, well known in the art at the time of the invention. McGall et al. teaches "Provided that the spatial location of each probe in an array is known, the data from the probes is collected and processed to yield the sequence of a target irrespective of the physical arrangement of the probes on a chip." (Col. 15 lines 55-59). It would have therefore been obvious to place the microarray into quadrants because the target was detectable as long as the area of the microarray was known. Furthermore, the amount of quadrants and probes on the array was well known and it would have been obvious that the range given would have worked with the array of McGall.

It would have been obvious to one of ordinary skill in the art to measure the level of fluorescence of a sample before and after hybridization. This would have been obvious because it was well known that this would have enabled one of ordinary skill to detect changes in the level of fluorescence due to hybridization.

It also would have been obvious to one of ordinary skill in the art at the time of the invention that labeled probe may be achieved by a non-amplification step. This would have been obvious because it was well known that probe may have arisen from genomic samples without the need of amplification.

3. Claim 6 and 37, 39-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over McCasky and McGall et al as applied to claims above, and further in view of Gelfland et al. (USPN 5,804,375).

The teachings of McCasky and McGall et al. were discussed above.

McGall et al. does not teach 2-amino purine as the nucleotide analog.

Gelfland et al. teaches "...2-amino purine...is another analog that could be used in probe synthesis. The probes containing such nucleotide derivatives may be hydrolyzed to release much more strongly fluorescent mononucleotides..." (Col. 12, line 35).

It would have been obvious to one of ordinary skill in the art at the time of the invention that the nucleotide analog of McGall may have been 2-amino purine. This is because it was a well known nucleotide analog at the time of the invention, and was useful in that it produced a strong fluorescent signal when hydrolyzed. For this reason it would have been obvious to one of ordinary skill in the art to use it with the invention of McGall.

4. Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over McCasky in view of McGall as applied to claims above, and further in view of Scholin et al. (USPN 6,187,530 B1).

The teachings of McCasky and McGall et al. are disclosed above.

McGall et al. does not teach an amino acid probe.

Scholin et al. teach antibody probes (Col. 9, line 59), which, of course, are comprised of amino acids, on an array.

It would have been obvious to one of ordinary skill in the art at the time of the invention that the probe of claim 1 may have been comprised of amino acids. This is because amino acid probes were well known in the art at the time of the invention and it

was well known that they were capable of being used with an array, as in the one disclosed by Scholin et al.

5. Claims 14 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over McCasky over McGall as applied to claims above, and further in view of Mandecki (USPN 6,001,571).

The teachings of McCasky and McGall et al. are disclosed above.

McGall does not teach that the bead is ferromagnetic, or the amount of probes contained thereon.

Mandecki teaches "In solid phase assays, small beads...are used to capture the analyte. Solid-phase microparticles may be made of different materials, such as glass...Some beads are made of ferromagnetic materials to facilitate their separation from complex suspensions of mixtures." (Col. 1 lines 20-26).

It would have been obvious to one of ordinary skill in the art at the time of the invention that the bead of McGall et al. may have been made up of ferromagnetic material, in order to facilitate its separation from complex suspension of mixtures. It would also have been obvious that a wide range in the number of probes attached to the beads may have been used, as this was well known in the art at the time of the invention.

6. Claim 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over McCasky in view of McGall as applied to claim 17 above, and further in view of Heagy et al. (USPN 5,753,516).

The teachings of McCasky and McGall are disclosed above.

Neither McCasky nor McGall teaches the use of a flow cytometer (Col. 17, bridging col. 18).

Heagy et al. teaches the use of flow cytometry in detecting fluorescence.

It would have been obvious to combine these teachings as it was well known in the art that flow cytometry was capable of detecting fluorescence. It would have been obvious to use flow cytometry because it would have been useful in detecting the amount of fluorescence within a sample and gave specific numeric results which would have been comparable to one another.

Summary

7. Claims 34-35 are objected to. Claims 1, 2, and 22-31 are rejected under 35 U.S.C. 102(e) as being anticipated by McCasky et al. Claims 1, 4, 5, 10-13, 16-17, 19-20, 22-27, 29-32, and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over McCasky in view of McGall et al. Claims 6 and 37, 39-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over McCasky and McGall et al as applied to claims above, and further in view of Gelfland et al. Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over McCasky in view of McGall as applied to claims above, and further in view of Scholin et al. Claims 14 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over McCasky over McGall as applied to claims above, and further in view of Mandecki. Claim 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over McCasky in view of McGall as applied to claim 17 above, and further in view of Heagy. No claims are allowable.

Response to Arguments

Applicant has argued that the 103 rejection of McCasky et al. is improper because the labels taught and considered by McCasky are limited to labels that are bound to DNA, that is, tags such as HRP and PA, etc. and not to labeled probe molecules, said labeled probe molecules having incorporated nucleotide analogs that fluoresce and whose fluorescence is utilized to measure or detect the presence or hybridization of complementary molecules, as presently claimed. However, this is why the art of McGall was relied upon, since McGall et al do teach the use of nucleotide analogs. The motivation for combining these references, as cited above, is that McGall teaches that "oligonucleotide analogues are resistant to hydrolysis or degradation by nuclease enzymes such as RNase A." This would have protected the probe from degradation.

Applicant further argues that McGall teaches away from the present invention, because McGall teaches the labeling of target molecules and not probes. However, this is why the references of McCasky and McGall were combined. Applicant states that there is no motivation to combine the references, as "the references themselves must provide some teaching whereby the applicant's combination would have been obvious." This motivation was provided, as discussed in the paragraph above. Applicant has argued that impermissible hindsight was used in the combination of the references. However, "[a]ny judgement on obviousness is in a sense necessarily a reconstruction based on hindsight reasoning, but so long as it takes into account only knowledge which was within the level of ordinary skill in the art at the time the claimed invention was made and does not include knowledge gleaned only from applicant's disclosure, such a

reconstruction is proper." In re McLaughlin 443 F.2d. It is Examiner's contention that it was within the level of ordinary skill in the art at the time the claimed invention was made to use nucleotide analogs in the probe molecule.

Conclusion

Any inquiries of a general nature relating to this application, including information on IDS forms, status requests, sequence listings, etc. should be directed to the Patent Analyst, Chantae Dessau, whose telephone number is (703) 605-1237.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janell Taylor Cleveland, whose telephone number is (703) 305-0273.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached at (703) 308-1152.

Papers related to this application may be submitted by facsimile transmission. Papers should be faxed to Group 1634 via the PTO Fax Center using (703) 872-9306 or 872-9307 (after final). The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG (November 15, 1989.)

Janell Taylor Cleveland

September 6, 2002

W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600